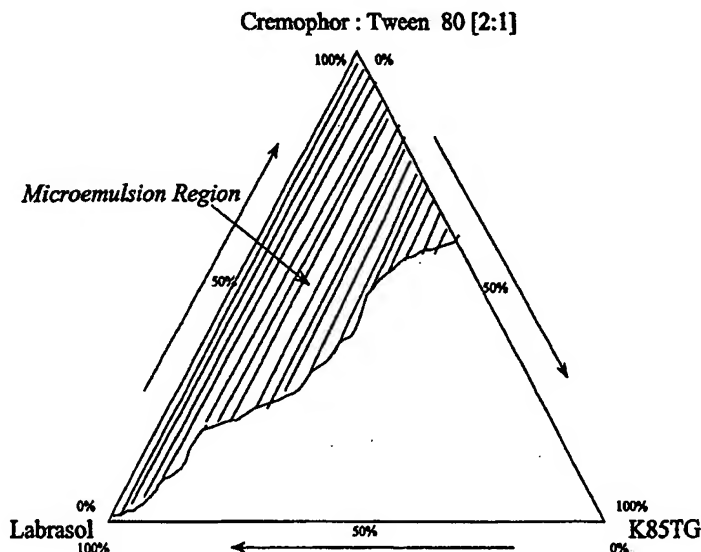




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/20	A1	(11) International Publication Number: WO 99/29316 (43) International Publication Date: 17 June 1999 (17.06.99)
<p>(21) International Application Number: PCT/US98/26329</p> <p>(22) International Filing Date: 10 December 1998 (10.12.98)</p> <p>(30) Priority Data: 08/988,270 10 December 1997 (10.12.97) US 60/084,516 7 May 1998 (07.05.98) US</p> <p>(71) Applicants (for all designated States except US): SEVERSON, Mary, L. [US/US]; 3295 Dundee Ridge Way, Duluth, GA 30096 (US). CYCLOSPORINE THERAPEUTICS LIMITED [IE/IE]; 2 Harbourmaster Place, Custom House Dock, Dublin 1 (IE).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): MISHRA, Awadhesh, K. [IN/CA]; Apartment #201, 670 Rue De Gaspe, Nuns Island (Verdum), Quebec H3E 1H8 (CA). RAMTOOLA, Zeibunnissa [IE/IE]; 163 Charlemont, Griffith Avenue, Dublin 9 (IE). MOUSSA, Iskandar [CA/CA]; Apartment #108, 4850 Cote-des-Neiges, Montreal, Quebec (CA). CLARKE, Nuala, M. [IE/IE]; 70 Castlesfield Court, Clonsilla, Dublin 15 (IE).</p> <p>(74) Agent: SEVERSON, Mary, L.; 1300 Gould Drive, Gainesville, GA 30504 (US).</p>	<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published With international search report.</p>	

(54) Title: PHARMACEUTICAL COMPOSITIONS CONTAINING AN OMEGA-3 FATTY ACID OIL



(57) Abstract

Self-emulsifying microemulsion or emulsion preconcentrate pharmaceutical compositions containing an omega-3 fatty acid oil such as a fish oil and a poorly water soluble therapeutic agent such as cyclosporin are formulated for administration, particularly oral administration to a human. The preconcentrates, which are substantially free of or contain only minor amounts of a hydrophilic solvent system, contain a pharmaceutically effective amount of an omega-3 fatty acid oil; a therapeutically effective amount of a poorly water soluble therapeutic agent that is substantially soluble in the omega-3 fatty acid oil; and a surfactant system comprising at least one surfactant. Microemulsions or emulsions formed by diluting the self-emulsifying preconcentrate with an aqueous solution are also provided.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

PHARMACEUTICAL COMPOSITIONS CONTAINING AN OMEGA-3 FATTY ACID OIL

FIELD OF THE INVENTION

The present invention relates to pharmaceutical compositions
5 containing an omega-3 fatty acid oil and a therapeutic agent. In particular,
the present invention relates to the administration, particularly oral, of self-
emulsifying microemulsion and emulsion preconcentrate formulations or
microemulsions and emulsions which contain omega-3 fatty acid oil and a
poorly water soluble therapeutic agent, for example, cyclosporin. Preferably,
10 the omega-3 fatty acid oil and therapeutic agent exert an additive or
synergistic therapeutic effect or the omega-3 fatty acid oil mediates the
negative side effects of the therapeutic agent.

BACKGROUND OF THE INVENTION

Omega-3 fatty acid oils possess properties that can be used for
15 numerous therapeutic advantages, including treatment of autoimmune and
inflammatory diseases such as rheumatoid arthritis, psoriasis, inflammatory
bowel diseases such as Crohn's disease and ulcerative colitis;
immunosuppressive treatment; hypertension prophylaxis in normal humans
and in heart transplant patients; coronary heart disease; hyperlipidemia;
20 hypertriglyceridemia; improvement of renal function and nephrotoxicity
reduction. US 4,678,808 describes the use of these oils to treat disorders
associated with arachidonic acid metabolites, including autoimmune
syndromes, acute and chronic inflammatory diseases, atherosclerosis, stroke,
myocardial infarction, deep vein thrombosis, surgery, hyperlipidaemic states,
25 hypertension, enhanced platelet responsiveness, vascular lesions and
occlusions, vascular spasm and diabetes. According to US 5,225,441, which
describes compositions for treating gingivitis and periodontitis, omega-3
polyunsaturated fatty acids compete with omega-6 polyunsaturated fatty acids
as a substrate in the arachidonic acid cascade and can therefore alter the
30 synthesis of prostaglandin and leukotrienes, both of which are powerful
mediators of inflammation and immune response. Other uses of omega-3

fatty acid oils are described in US 5,034,415 (diabetes mellitus), US 4,843,095 (rheumatoid arthritis), JP 2253629 (anticancer), US 4,879,312 (enhancing angiogenesis), JP 1290625 (improvement of cerebral function), EP 378,824 (anti-cachexia, cholesterol and triglyceride levels reduction, platelet aggregation inhibition, colon adenocarcinomas growth inhibition), US 5,457,130 (cancer cachexia, malignant tumors, abnormal cAMP levels in adipose tissue, lipolytic activity inhibition) and US 5,436,269 (hepatitis).

Cyclosporins are an example of a class of drugs that is soluble in omega-3 fatty acid oil and capable of exerting an additive or synergistic therapeutic effect with the omega-3 fatty acid oil. Alternatively, the omega-3 fatty acid oil mediates the negative side effects, such as nephrotoxicity, of a cyclosporin such as cyclosporin A.

Cyclosporin A (CyA) is a lipophilic cyclic undecapeptide that can be isolated from the fungus *Tolypocladium inflatum* Gams and which produces calcium dependent, specific and reversible inhibition of transcription of interleukin-2 and several other cytokines, most notably in T helper lymphocytes. Because of its immunosuppressive properties, it is widely used as first line therapy in the prophylaxis and treatment of transplant rejection (e.g., allo- or xeno-transplant rejection such as in patients receiving heart, lung, combined heart-lung, liver, kidney, pancreatic, skin or corneal transplants) and various autoimmune and inflammatory diseases. CyA is used in the treatment of multi-drug resistance syndrome, for example in patients undergoing chemotherapy or following organ transplantations. In patients with severe disease refractory to standard treatment; CyA is an effective therapy in acute ocular Behcet's syndrome; endogenous uveitis; psoriasis; atopic dermatitis; arthritis, particularly rheumatoid arthritis; active Crohn's disease and nephrotic syndrome. Other conditions include arthritis chronica progrediente and arthritis deformans, autoimmune hematological disorders including hemolytic anemia, aplastic anemia, pure red-cell anemia and idiopathic thrombocytopenia, systemic lupus erythematosus, polychondritis, scleroderma, Wegener granulomatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, Steven-John syndrome, idiopathic sprue, autoimmune inflammatory bowel disease, e.g., ulcerative colitis, endocrine ophthalmology, Graves disease, sarcoidosis, multiple sclerosis,

primary biliary cirrhosis, juvenile diabetes, keratoconjunctivitis sicca and vernal keratoconjunctivitis, interstitial lung fibrosis, psoriatic arthritis, glomerulonephritis, juvenile dermatitis, asthma, tumors, hyperproliferative skin disorders and fungal infections. This drug has also been used to treat patients
5 with moderate or severe aplastic anemia who are ineligible for bone marrow transplantation and those with primary biliary cirrhosis. CyA may be effective in patients with intractable pyoderma gangrenosum, polymyositis/dermatomyositis or severe, corticosteroid-dependent asthma. CyA is known to have a very specific effect on T-cell proliferation although the
10 precise mechanism remains unclear. A number of non-immunosuppressive analogues of cyclosporin A have been shown to have resistance modifier activity and some are more potent than the parent compound. Nephrotoxicity, hepatotoxicity, hypertension, headache, hypertrichosis, gingival hyperplasia, neurological and gastrointestinal effects, thrombocytopenia and
15 microangiopathic hemolytic anemia, hyperkalemia and hyperuricemia and development of skin and lymphoproliferative malignancies are the most common adverse events in cyclosporin recipients.

CyA and fish oils have been administered concurrently to organ transplant patients in various clinical trials. For instance, Andreassen *et al.*
20 (JAAC, 29(6):1324-31 (1997)) reported effective hypertension prophylaxis in heart transplant patients who were given cyclosporin A and 4g of fish oil. Cyclosporin A-treated and fish oil fed renal transplant recipients had improved renal function following a rejection episode (*Transplantation*, 54:257 (1992)). US 5,118,493 describes the administration of CyA together with an omega-3
25 fatty acid oil to mediate the nephrotoxic effects of the cyclosporin.

Certain oil mixtures of lipophilic drugs such as a cyclosporin with vegetable oils or other lipidic substances, surface active agents, solvents and other excipients are known to spontaneously produce dispersions of very low mean particle size (such as <200 nm) when mixed with an aqueous medium.
30 These dispersions are known as microemulsions and the oily mixtures that produce the microemulsions are popularly referred to as microemulsion preconcentrates. Upon oral delivery, the microemulsion preconcentrates are thought to produce similar dispersions of very low particle size with gastric and other physiological fluids.

Cyclosporins are highly lipophilic, poorly water soluble and, therefore, have been supplied as an olive oil or peanut oil solution for clinical use. However, the bioavailability of cyclosporin from such oily solutions is very low and gives rise to great intersubject variation with reported systemic availability ranging from 4 to 25% (Takada, K. et al, *J. Pharmacobio-Dyn.*, 11:80-7 (1988)). The bioavailability of cyclosporin has been reported to be dependent on food, bile and other interacting factors (*Clin. Pharmacokinetics*, 24:472-95 (1993)). A widely used commercial formulation of CyA, SANDIMMUNE® for oral administration, is a solution of cyclosporin A in vegetable oil derivatives containing some other inactive excipients. Very high inter- and intra-patient and food dependent variability in the bioavailability of CyA has been observed from this formulation. The commercial microemulsion preconcentrate formulation, NEORAL®, has been claimed to provide high bioavailability for CyA with low inter-and intra-patient variability. However, risks of adverse drug reactions have been indicated on switching to Neoral® (see, e.g., *Drug Saf*, 16:366-73 (1996); *Lancet*, 348:205 (1996)).

Numerous microemulsion preconcentrate formulations are known, including soft gel formulations, for enhancing the solubilization and oral bioavailability of a poorly water soluble drug compound such as cyclosporine. Typically, these formulations include an active agent, an oil component, a surfactant to emulsify the formulation and a hydrophilic solvent/co-surfactant system to solubilize the active agent. Typical solvent/co-surfactant systems include ethanol, polyethylene glycols, propylene carbonate, dimethylisobutylate, Transcutol and/or Glycofurol. Disadvantages of these formulations include stability or precipitation problems caused by migration of volatile hydrophilic solvents or cosolvents (e.g., ethanol can permeate a gelatin shell at normal storage temperatures), stability or precipitation problems caused by hygroscopic solvents or co-surfactants (e.g., propylene glycols, Transcutol, Glycofurol), and toxicity problems caused by addition of certain solvents or co-surfactants (e.g., dimethylisobutylate).

Typically, the oil component of a conventional microemulsion consists of fatty acid mono-, di- or triglycerides from a vegetable oil; medium chain triglycerides and/or mono- or di-glycerides; mixtures of glycerides and polyglycolized glycerides; tocopherols, and/or tocotrienols; or

hydrophobic alcohols. US 5,603,951 describes a microemulsion concentrate containing cyclosporin as an active ingredient, dimethylisorbide as a required co-surfactant, a surfactant, and an oil which can be refined fish oil, these components being present in the ratio of 1:1-5:2-10:1-5. The inventors
5 of the '951 patent added dimethylisorbide, which is a solvent available under the Tradename ARLASOVE®, to the formulation to address the disadvantages listed above for prior solvents/co-surfactants systems such as ethanol, Transcutol, or Glycofurol. The '951 preconcentrates are formed by dissolving the cyclosporin in the dimethylisorbide at a temperature of
10 approximately 60°C followed by addition of the oil component and the surfactant.

It is an object of the present invention to provide a stable, self-emulsifying microemulsion or emulsion preconcentrate formulation and/or a microemulsion or emulsion containing an omega-3 fatty acid oil that is
15 capable of enhancing the bioavailability of a poorly water soluble therapeutic agent while minimizing the inter- and intra-patient or food variability in the bioavailability of the therapeutic agent. A further object is to provide self-emulsifying preconcentrates or corresponding microemulsions and emulsions having increased therapeutic agent dosing reproducibility compared to
20 conventional formulations. An additional object is to provide self-emulsifying preconcentrates or corresponding microemulsions or emulsions containing an omega-3 fatty acid oil and a poorly water soluble therapeutic agent in which the bioavailability and dosing reproducibility of both the omega-3 fatty acid oil and the therapeutic agent is high.

25 It is an additional object of this invention to provide a stable self-emulsifying microemulsion or emulsion preconcentrate formulation and/or a microemulsion or emulsion in which the omega-3 fatty acid oil and the therapeutic agent exert an additive or synergistic therapeutic effect or the omega-3 fatty acid oil mediates the negative side effects of the therapeutic
30 agent.

A further object of this invention is to provide a stable self-emulsifying preconcentrates and/or a microemulsion or emulsion in which the poorly water soluble therapeutic agent is substantially soluble in the omega-3 fatty

acid oil, thus eliminating or drastically reducing the need for substantial amounts of a hydrophilic solvent system.

A further object of this invention is to provide a stable self-emulsifying microemulsion or emulsion preconcentrate formulation and/or a
5 microemulsion or emulsion containing an omega-3 fatty acid oil and a poorly water soluble therapeutic agent which is suitable for formulation into soft or hard capsules for oral administration.

A still further object of this invention is to provide a stable self-emulsifying microemulsion or emulsion preconcentrate soft or hard capsule
10 formulation containing an omega-3 fatty acid oil and a poorly water soluble therapeutic agent having relatively high therapeutic amounts of both the omega-3 fatty acid oil and the poorly water soluble therapeutic agent.

SUMMARY OF THE INVENTION

Surprisingly, it has been found that stable, self-emulsifying
15 microemulsion or emulsion preconcentrates comprising a poorly water soluble drug can be formed using an omega-3 fatty acid oil to substantially solubilize the poorly water soluble drug. The solubilizing properties of the omega-3 fatty acid oil eliminate or drastically reduce the need for substantial amounts of a hydrophilic solvent/co-solvent system, also allowing for formulation of
20 preconcentrates that are substantially free of a hydrophilic solvent/co-solvent system or contain only minor amounts of a hydrophilic solvent/co-solvent system. It was also found that the solubility of a poorly water soluble drug was enhanced in oils containing a mixture of omega-3 fatty acid oils, thus allowing formulation of preconcentrates containing relatively higher quantities
25 of the poorly water soluble drug. The self-emulsifying microemulsion and emulsion preconcentrates according to the instant invention take the form of a poorly water soluble therapeutic agent substantially solubilized in an omega-3 fatty acid oil that is capable of being self-emulsified by a surfactant system comprising at least one surfactant when the preconcentrate is diluted with an
30 aqueous medium.

Thus, the present invention provides a self-emulsifying preconcentrate pharmaceutical composition suitable for administration to a mammal, particularly oral administration to a human, and capable of forming an oil-in-water microemulsion or emulsion upon dilution with an aqueous solution,

5 comprising

(a) a pharmaceutically effective amount of an omega-3 fatty acid oil;

(b) a therapeutically effective amount of a poorly water soluble therapeutic agent, wherein the poorly water soluble therapeutic agent is substantially soluble in the omega-3 fatty acid oil; and

10 (c) a surfactant system comprising at least one surfactant;

wherein the composition contains minor amounts or is substantially free of a hydrophilic solvent system. The present invention also provides microemulsions or emulsions formed by diluting a self-emulsifying preconcentrate with an aqueous solution.

15

Compositions according to this invention that are substantially free or contain only minor amounts of a hydrophilic solvent system avoid the disadvantages of the prior art systems given above.

The therapeutic agent, which is substantially soluble in the omega-3 fatty acid oil, is beneficially co-administered with the omega-3 fatty acid oil to achieve, for instance, greater bioavailability or less variation in the bioavailability of the therapeutic agent, an additive therapeutic effect with the omega-3 fatty acid oil, a synergistic therapeutic effect with the omega-3 fatty acid oil, or a reduction in at least one side effect of the therapeutic agent.

25 Thus, the present invention also encompasses methods for lowering the therapeutically effective amount of a poorly water soluble therapeutic agent by administering to a human in need of a therapeutically effective amount of the therapeutic agent the self-emulsifying preconcentrates or the microemulsions/emulsions of the present invention. Further, the present invention encompasses methods for reducing the side effects of a poorly water soluble therapeutic agent by administering to a human in need of a therapeutically effective amount of the therapeutic agent the self-emulsifying preconcentrates or the microemulsions/emulsion of the present invention.

30

A preferred therapeutic agent is a cyclosporin, particularly cyclosporin

- A. Preferred omega-3 fatty acid oils include omega-3 free fatty acids, omega-3 fatty acid triglycerides and omega-3 fatty acid ethyl esters, such as EPA, DHA, triglycerides of EPA, triglycerides of DHA, ethyl esters of EPA, ethyl esters of DHA and mixtures thereof.

Oils containing high concentrations of omega-3 fatty acid oils such as fish oils or their mixtures are particularly useful for forming self-emulsifying preconcentrates, microemulsions or emulsions according to the present invention. Preferably, the oil is fish oil containing at least 50%, preferably at least 70%, more preferably at least 80% omega-3 fatty acid oil to obtain a pharmaceutically effective amount of an omega-3 fatty acid oil in a minimal volume. Because of the solubility of the therapeutic agent in the oil or mixture of oils containing omega-3 fatty acid oil, self-emulsifying preconcentrate, microemulsion or emulsion compositions containing both a therapeutically effective amount of the therapeutic agent and an amount of omega-3 fatty acid oil needed to achieve beneficial co-administration with the therapeutic agent can be formulated with minimal added excipients.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a pseudo-ternary phase diagram for the placebo system described in Example 8 upon a 1 to 20 dilution of the preconcentrate with water. The diagram plots the relative concentration of Labrasol (0 to 100%), the concentration of the omega-3 fatty acid oil K85TG (0 to 100%), and the concentration of Cremophor RH40:Tween 80 in a 2:1 ratio (0 to 100%) for the placebo system. The relative concentration of Labrasol increases from 0% at the lower right hand margin of the diagram to 100% at the lower left corner; the relative concentration of Cremophor RH40:Tween 80 in a 2:1 ratio increases from 0% at the baseline of the diagram to 100% at the apex; and the relative concentration of K85TG increases from 0% at the apex to 100% at the lower right hand corner of the diagram. The shaded area identifies those compositions having C1, C1/C2 or C2 clarity as the microemulsion region for a 1 to 20 dilution of the preconcentrate with water; and

Figure 2 shows a pseudo-ternary phase diagram for the 100 mg CyA system described in Example 8 upon a 1 to 20 dilution of the preconcentrate with water. The diagram plots the relative concentration of Labrasol (0 to 100%), the concentration of the omega-3 fatty acid oil K85TG (0 to 100%), and the concentration of Cremophor RH40:Tween 80 in a 2:1 ratio (0 to 100%) for compositions containing 100 mg CyA. The relative concentration of Labrasol increases from 0% at the lower right hand margin of the diagram to 100% at the lower left corner; the relative concentration of Cremophor RH40:Tween 80 in a 2:1 ratio increases from 0% at the baseline of the diagram to 100% at the apex; and the relative concentration of K85TG increases from 0% at the apex to 100% at the lower right hand corner of the diagram. The shaded area identifies those compositions having C1, C1/C2 or C2 clarity as the microemulsion region for a 1 to 20 dilution of the preconcentrate with water.

15 DETAILED DESCRIPTION OF THE INVENTION

As used herein, the term "omega-3 fatty acid oil" means a natural or synthetic omega-3 fatty acid, and pharmaceutically acceptable esters, derivatives, precursors or salts thereof and mixtures thereof. Examples of omega-3 fatty acid oils include but are not limited to omega-3 polyunsaturated, long-chain fatty acids such as a eicosapenta-5,8,11,14,17-enoic acid (hereinafter "EPA"), docosahexa-4,7,10,13,16,19-enoic acid (hereinafter "DHA"), and α -linolenic acid; esters of an omega-3 fatty acid with glycerol such as mono-, di- and triglycerides; esters of the omega-3 fatty acid and a primary alcohol such as fatty acid methyl esters and fatty acid ethyl esters; precursors of an omega-3 fatty acid oil, such as EPA and DHA precursor α -linolenic acid; and derivatives such as polyglycolized derivatives or polyoxyethylene derivatives. Preferred omega-3 fatty acid oils are EPA or DHA, triglycerides thereof, ethyl esters thereof and mixtures thereof. The omega-3 fatty acids or their esters, derivatives, precursors, salts and mixtures thereof can be used either in their pure form or as a component of an oil such as fish oil (otherwise known as marine oil), preferably highly purified fish oil concentrates, or perilla oil or marine microalgae oil. Suitable fish oils are, for example, those types which are recovered in substantial quantities from cold-water fish, such as pilchard oil, menhaden oil, Peruvian fish oil, sardine oil,

salmon oil, herring oil, and mackerel oil. Preferably, the fish oil has a high omega-3 fatty acid oil content, such as 50% or higher, more preferably, 70% or higher, most preferably 80% or higher. Examples of suitable omega-3 fatty acid oils include the following oils available from Croda Oleochemicals
5 (England): Incromea TG3525 (35:25 EPA:DHA ratio; triglycerides), Incromea E5015 (50:15 EPA:DHA ratio; ethyl esters) and the following oils available from Pronova Biocare (Sandefjord, Norway): EPAX6000FA, EPAX5000TG, EPAX4510TG, EPAX2050TG, K85TG, K85EE, K80EE and EPAX7010EE (further details listed in Table 1 herein). Preferred mixtures
10 include mixtures of fatty acid ethyl esters and fatty acids; fatty acid ethyl esters and fatty acid triglycerides; fatty acids and fatty acid triglycerides; and fatty acid esters, fatty acid triglycerides and fatty acids such as mixtures containing K85EE and EPAX6000FA; EPAX5000TG and EPAX6000FA; K85EE and EPAX5000TG; and K85EE, EPAX6000FA and EPAX5000TG.

15 As used herein, the term "therapeutic agent" means a poorly water soluble drug or a mixture of poorly water soluble drugs that can be beneficially co-administered with an omega-3 fatty acid oil to a mammal, especially a human. By "poorly water soluble drug" is meant a drug that is insoluble in water or has an aqueous solubility of less than about 5 part per
20 1000 parts of water by weight at 20°C. Examples of beneficial co-administration include co-administration that results in at least one synergistic therapeutic effect or at least one additive therapeutic effect between the therapeutic agent and the omega-3 fatty acid oil; co-administration in which the omega-3 fatty acid oil mediates at least one negative side effect of the
25 therapeutic agent and co-administration in which the omega-3 fatty acid oil solubilizes the therapeutic agent to allow for greater bioavailability and/or reduced variation in the bioavailability of the therapeutic agent. For instance, in addition to other beneficial co-administration effects, omega-3 fatty acid oil reduces the nephrotoxicity of cyclosporin when co-administered, allowing
30 treatment with higher levels of cyclosporin and producing a greater clinical response at a given dose of cyclosporin.

Examples of therapeutic agents include nephrotoxic drugs such as cyclosporins and amphotericin B; cardiotoxic drugs such as amphotericin B and FK506; drugs with immunosuppressive effects or anti-inflammatory drugs

such as drugs for treating rheumatology, arthritis, psoriasis, inflammatory bowel disease, Crohn's disease or demyelinating diseases including multiple sclerosis; anti-tumor drugs such as melphalan, chlormethine, extramustinephosphate, uramustine, ifosfamide, mannomustine, trifosfamide, streptozotocin, mitobronitol, methotrexate, fluorouracil, cytarabine, tegafur, idoxide, taxol, paclitaxel, daunomycin, daunorubicin, bleomycin, amphotericin; hyperlipidemia or hypercholesterolemia drugs such as fenofibrate; dioplar disease drugs; drugs which increase lipids and/or triglyceride levels; and drugs for treating Alzheimer's disease. The therapeutic agent can be selected from a variety of known classes of drugs including, but not limited to, analgesics, anti-allergic agents, anti-fungals, anti-inflammatory agents, anti-arrhythmic agents, antibiotics, anticoagulants, antidepressants, antidiabetic agents, anti-epilepsy agents, antihypertensive agents, anti-gout agents, anti-malarials, anti-migraine agents, antimuscarinic agents, antineoplastic agents, anti-protozoal agents, anxiolytics, thyroids, anti-thyroids, antivirals, anoretics, bisphosphonates, cardiac inotropic agents, cardiovascular agents, corticosteroids, diuretics, dopaminergic agents, gastrointestinal agents, hemostatics, histamine receptor antagonists, hypnotics, immunosuppressants, kidney protective agents, lipid regulating agents, muscle relaxants, neuroleptics, neurotropic agents, opioid agonists and antagonists, parasympathomimetics, protease inhibitors, prostaglandins, sedatives, sex hormones, stimulants, sympathomimetics, vasodilators and xanthins. The therapeutic agent may comprise a mixture of poorly water-soluble drugs that can be beneficially co-administered with an omega-3 fatty acid oil.

As used herein, the term "a pharmaceutically effective amount of an omega-3 fatty acid oil" means an amount effective either 1) to solubilize a therapeutically effective unit dose amount of the poorly water soluble therapeutic agent; 2) to exert an additive therapeutic effect in combination with the poorly water soluble therapeutic agent; 3) to exert a synergistic therapeutic effect in combination with the poorly water soluble therapeutic agent; or 4) to mediate, such as decrease, at least one negative side effect of the therapeutic agent. Typically, the amount of omega-3 fatty acid oil in a unit dose of the self-emulsifying microemulsion or emulsion concentrate and/or microemulsion or emulsion can be adjusted so that the daily dose of the

omega-3 fatty acid oil is from about 1.0 g to about 6.0 g in humans per day, preferably from about 2.0 g to about 5.0 g, most preferably about 2.5 g to about 4.0 g per day. Alternatively, the typical dosage of the omega-3 fatty acid oil ranges from about 14 to 86 mg/kg/day; the typical dosage of a fish oil
5 contains an equivalent amount of omega-3 fatty acid oil. Preferably, the unit dose amount for an oil containing the omega-3 fatty acid oil ranges from about 5% to 70% of the microemulsion or emulsion preconcentrate.

As used herein, the term "surfactant" means a non-ionic or ionic surfactant having an HLB less than about 20. Suitable surfactants include but
10 are not limited to polyoxyethylene glycolated natural or hydrogenated vegetable oils; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene fatty acid esters; polyoxyethylene alkyl ethers; polyethylene glycol mono- and di- fatty acid esters; transesterification product of natural vegetable oil triglyceride with polyalkylene polyol; and fatty alcohol ethoxylates. Examples
15 of suitable surfactants include Cremophor-RH40, Cremophor-RH60, Cremophor-EL, Tween-20, Tween-40, Tween-60, Tween-65, Tween-80, Tween-85, Labrasol, Nikkol HCO-50, Nikkol HCO-40, Nikkol HCO-60, Brij 30, Gelucire 44/14, Gycerox 767, Imwitor 742, Imwitor 308, Imwitor 375, Labrafac Lipophile, Labrafac CM10, Tagat TO, Myrj 52, Myvacet 9-45, and Vitamin E-TPGS.
20

As used herein, the term "substantially soluble" in reference to the solubility of the poorly water soluble therapeutic agent in the omega-3 fatty acid oil means the poorly water soluble therapeutic agent is soluble in the omega-3 fatty acid oil or has a solubility of more than 1 part per 100 parts of
25 omega-3 fatty acid oil by weight at 20°C.

As used herein, the term "hydrophilic solvent system" means a system comprising a solvent or co-solvent (other than an omega-3 fatty acid oil) with respect to the poorly water soluble therapeutic agent and/or a co-surfactant having an HLB greater than about 20. Example hydrophilic solvent system
30 components include ethanol, alkylene glycols such as propylene glycol, polyethylene glycol, polyoxypropylene block copolymers, Glycofurol, Transcutol, dimethylisosorbide and mixtures thereof. Preferred hydrophilic solvent system components are 1,2-propylene glycol, ethanol and

polyethylene glycol having an average molecular weight of less than or equal to 1000, individually or in combination. More preferred hydrophilic solvent system components are 1,2-propylene glycol and ethanol, individually or in combination. As used herein, the term "minor amounts" as used in reference
5 to a hydrophilic solvent system means an amount less than about 10% by weight of the components present in the preconcentrate, preferably less than about 5% by weight, most preferably less than the amount of therapeutic agent present in the formulation.

The self-emulsifying microemulsion and emulsion preconcentrate and
10 microemulsion and emulsion formulations according to the present invention may optionally include minor amounts of a hydrophilic solvent system to increase the shelf life or stability of the preconcentrates. Other additives, such as antioxidants or preservatives, may also be present. Examples include tocopherol, tocopherols excipient, ascorbyl palmitate, butylated
15 hydroxyanisole or other antioxidants and preservatives listed in USP XXII, Pharmaceutical Ingredients.

The self-emulsifying preconcentrates and the microemulsions and emulsions of the instant invention can be adapted for oral administration. Preferred oral dosage forms for the preconcentrates include hard and softgel
20 capsules. Preformed microemulsions and emulsions are preferred oral dosage forms for the microemulsions and emulsions. The formulations according to the instant invention can also be administered by other routes of administration, including topical administration or parenteral administration such as i.v. or i.p. administration.

25 *Example 1 – Solubility of Cyclosporin in Fish Oils at Ambient Temperature*

The solubility at ambient temperature for cyclosporin A (CyA) was determined at ambient temperature for fish oils containing polyunsaturated omega-3 free fatty acid oil as free fatty acids (EPAX6000FA), omega-3 fatty acid glycerides (EPAX5000TG, EPAX4510TG, EPAX2050TG, and K85TG),
30 omega-3 fatty acid ethyl esters (K85EE, EPAX7010EE and K80EE) and in a mixture of free fatty acids and ethyl esters (EPAX6000FA/K85EE) (Pronova Biocare, Sandefjord, Norway). The K85TG is a mixed glyceride form

obtained by transesterification of K85EE with glycerol giving the resulting blend: K85 monoglyceride: 5-15%; K85 diglyceride: 20-30%; K85 triglyceride: 50-70% and K85EE remnants: <5%. Further details regarding these omega-3 fatty acid oils and the CyA solubilities are given in Table 1.

- 5 The solubility of CyA in various oils was found to be variable. A blend of K85EE with EPAX6000FA increased the solubilizing power for CyA greatly compared to either omega-3 fatty acid oil by itself. Furthermore, this CyA solution in a mixture of K85EE and EPAX 6000 remained in the form of a clear solution at low and high temperatures, such as 2-8°C and about 40°C.
- 10 No precipitation or crystallization occurred upon cooling to about -20°C for more than 24 hours. Thus, these initial findings indicate that CyA microemulsion preconcentrates made with this fish oil blend might have very good thermal stability over a wide temperature range.

TABLE 1

Fish Oil	Chemical Form	ω -3 content %	EPA %	DHA %	EPA to DHA ratio	Additives mg/g	Solubility mg CyA per g solvent
EPAX6000FA	free fatty acid	55-60	33	22	3:2	Vit A: 1 IU VitD: 1 IU VitE: 3-4.5	557mg/g
EPAX5000TG	glycerides	50	30	20	3:2	VitE: 3.0-4.5	584 mg/g
EPAX4510TG	glycerides	55	45	10	9:2	VitE: min3.0	443 mg/g
EPAX2050TG	glycerides	70	20	50	2:5		459 mg/g
K85TG	glycerides	80	45.9	33.3	1.38:1	VitE: 4.0	366 mg/g
K85EE	ethyl ester	84	46	38	1.2:1	Vit E: 3.2-4.8	225 mg/g
K80EE	ethyl ester	81	45	36	1:0.8	Vit E: 3.2-4.8	
EPAX7010EE	ethyl ester	82	70	12	5.8:1	Vit E: 2.1-3.2	265 mg/g
K85EE + EPAX6000FA (2:1 w/w)	ethyl ester + free fatty acid	73-76			~3:2		731mg/g

The solubility of CyA in various oils was found to be variable. A blend of K85EE with EPAX6000FA increased the solubilizing power for CyA greatly compared to either omega-3 fatty acid oil by itself. Furthermore, this CyA solution in a mixture of K85EE and EPAX 6000 remained in the form of a clear solution at low and high temperatures, such as 2-8°C and about 40°C. No precipitation or crystallization occurred upon cooling to about -20°C for more than 24 hours. Thus, these initial findings indicate that CyA microemulsion preconcentrates made with this fish oil blend might have very good thermal stability over a wide temperature range.

Example 2 – Preparation of Microemulsion/Emulsion Preconcentrates

To make the preconcentrate formulations, a solution containing the poorly water soluble therapeutic agent and the oil component containing the omega-3 fatty acid oil were prepared in appropriate proportions by adding the therapeutic agent in small increments and stirring. The surfactant system was prepared by mixing separately the chosen surfactants in their determined ratios. The oil component/therapeutic agent solution was then combined with the surfactant system solution to form the preconcentrate, with stirring for approximately 5 minutes with or without heating to 30-40°C until homogeneous. Alternatively, formulations according to the instant invention were prepared by simply combining the given amounts of the therapeutic agent, the given amounts of the oil component and the given amounts of the surfactant system with stirring until a homogeneous solution was formed. Alternatively, the therapeutic agent can be added to a mixture of the oil component and the surfactant system and stirred until a homogeneous solution was formed. To test the behavior of the preconcentrates upon contact with an aqueous system, the preconcentrate was diluted, such as 1:1, 1:10, 1:20, 1:50 or 1:100 v/v dilutions, with water to simulate conditions in the stomach.

As given in the examples below, a variety of surfactant systems were combined with various omega-3 fatty acid oils at varying ratios of the components and the resulting solutions were diluted 1:20 to determine the

component ratios that provide suitable microemulsion and emulsion pre-concentrate formulations. Clarity of the resulting solutions was classified as follows: C1 denotes a transparent solution; C2 denotes a translucent solution; C3 denotes a slightly opaque solution; and C4 denotes a milky white solution. Generally, the self-emulsifying microemulsion systems correspond to the C1 to C2 solutions and the self-emulsifying emulsion systems correspond to the C3 to C4 solutions. A pseudo-ternary phase diagram that maps the different clarity regions for a particular omega-3 fatty acid oil/surfactant system can be made to visualize the appropriate ratios of the components needed to form a microemulsion pre-concentrate or an emulsion pre-concentrate formulation.

Example 3 – K85EE / Cremophor RH40 / Labrasol

Samples were prepared according to Example 2 for the omega-3 fatty acid oil K85EE and a surfactant system comprising Labrasol and Cremophor RH40 with varying percentages for all three of these components. Table 2 charts the clarity values for this system (placebo) upon 1 to 20 dilution with water while Table 3 charts 1 to 20 dilution clarity values for the corresponding systems in which 25, 50, 100 and 150 mg of CyA per ml of solution were added. From an analysis of the placebo system, it appears that the greatest amount of oil possible in a microemulsion pre-concentrate formulation formulated according to this system is around 40-45% K85EE.

TABLE 2				
K85EE %	Labrasol %	Cremophor RH40%	CyA mg/ml	Clarity
5	62	33	n/a	C1
10	15	75	n/a	C1
12	45	43	n/a	C1
15	79	6	n/a	C4
20	38	42	n/a	C1/C2
22	65	13	n/a	C4
27	20	53	n/a	C1/C2
30	56	14	n/a	C4
40	10	50	n/a	C2
50	5	45	n/a	C4
55	10	35	n/a	C4

TABLE 3				
K85EE %	Labrasol %	Cremophor RH40%	CyA mg/ml	Clarity
5	62	33	25	C1
10	15	75	25	C1
12	45	43	25	C1
20	38	42	25	C1
5	62	33	50	C1
10	15	76	50	C1
12	45	43	50	C1
20	38	42	50	C1
5	62	33	100	C3
12	45	43	100	C1
20	38	42	100	C1
5	62	33	150	C4
12	45	43	150	C3
20	38	42	150	C2/C3

Example 4 – K85EE / Tween 80 / Labrasol

- 5 Samples were prepared according to Example 2 for the omega-3 fatty acid oil K85EE and a surfactant system comprising Labrasol and Tween 80 with varying percentages for all three of these components. Table 4 charts the clarity values upon 1 to 20 dilution with water for this system (placebo) while Table 5 charts the 1 to 20 dilution clarity values for corresponding systems in which 25 and 50 mg of CyA per ml of solution were added.

TABLE 4				
KE85EE %	Labrasol %	Tween 80 %	CyA mg/ml	Clarity
5	62	33	n/a	C1
10	15	75	n/a	C1
12	45	43	n/a	C1/C2
15	79	6	n/a	C4
20	38	42	n/a	C1/C2
22	55	13	n/a	C4
27	20	53	n/a	C1/C2
30	56	14	n/a	C4
40	5	55	n/a	C2/C3
50	5	45	n/a	C2/C3
53	12	35	n/a	C4

TABLE 5				
K85EE %	Labrasol %	Tw en 80%	CyA mg/ml	Clarity
5	62	33	25	C2
10	15	75	25	C1
12	45	43	25	C1/C2
20	38	42	25	C2
27	53	20	25	C2
40	5	55	25	C2/C3
50	5	45	25	C4
5	62	33	50	C4
10	15	75	50	C1/C2
12	45	43	50	C2/C3
20	38	42	50	C3
27	53	20	50	C2/C3

Comparison between the K85EE/Cremophor RH40/Labrasol system of Example 3 and the K85EE/Tween 80/Labrasol system of Example 4 shows that while the placebo systems are similar, as cyclosporin is added to the system, the K85EE/Cremophor RH40/Labrasol system provides a larger microemulsion region when plotted on a pseudo-ternary phase diagram.

Example 5 – K85EE / Cremophor RH40 / Tween 80 / Labrasol

Samples were prepared according to Example 2 for the omega-3 fatty acid oil K85EE and a surfactant system comprising Labrasol, Tween 80 and Cremophor RH40 (holding the ratio of Cremophor RH40 to Tween 80 at 2:1) with varying percentages of K85EE, Labrasol and Tween 80/Cremophor RH40. Table 6 charts the 1 to 20 dilution clarity values for this system (placebo) as well as the corresponding system with 5% Ethanol included. Table 7 charts 1 to 20 dilution clarity values for corresponding systems in which 100 mg of CyA per ml of solution has been added.

TABLE 6					
K85EE %	Labrasol %	Cr mophor RH40:Tween 80 (2:1) %	Ethanol %	CyA mg/ml	Clarity
21.7	0	78.3	n/a	n/a	C1
21.7	12.6	66.7	n/a	n/a	C1
21.7	20.8	67.5	n/a	n/a	C1
31	0	69	n/a	n/a	C1/C2
31	11	68	n/a	n/a	C1/C2
31	18.4	60.6	n/a	n/a	C1/C2
38.8	0	61.2	n/a	n/a	C1/C2
38.8	9.9	51.3	n/a	n/a	C1/C2
38.8	16.2	48	n/a	n/a	C1/C2
42.5	10.5	47	n/a	n/a	C1/C2
44	5	51	n/a	n/a	C2
48.5	0	51.5	n/a	n/a	C2
48.5	8.2	43.3	n/a	n/a	C2
48.5	13.7	37.8	n/a	n/a	C2
21.7	0	78.3	5%	n/a	C1
21.7	12.6	66.7	5%	n/a	C1
21.7	20.8	67.5	5%	n/a	C1
31	0	69	5%	n/a	C1/C2
31	11	68	5%	n/a	C1/C2
31	18.4	60.6	5%	n/a	C1/C2
38.8	0	61.2	5%	n/a	C1/C2
38.8	9.9	51.3	5%	n/a	C1/C2
42.5	10	47.5	5%	n/a	C1/C2
44	5	51	5%	n/a	C1/C2
48.5	0	51.5	5%	n/a	C1/C2
48.5	8.2	43.3	5%	n/a	C2
48.5	13.7	37.8	5%	n/a	C2
52.5	5	42.5	5%	n/a	C2

Tables 6 and 7 show that inclusion of 5% ethanol compared to the same system without ethanol provides similar microemulsion region sizes for both placebo systems (20% to 50% oil) and the corresponding 100 mg/ml CyA systems.

TABLE 7					
K85EE %	Labrasol %	Cremophor RH40:Tween 80 (2:1) %	Ethanol %	CyA mg/ml	Clarity
42.5	10	47.5	n/a	100	C1/C2
44	6	51	n/a	100	C1/C2
46	5	49	n/a	100	C1/C2
46.5	11.5	42	n/a	100	C1/C2
47	0	53	n/a	100	C1/C2
53	8	42	n/a	100	C2/C3
42.5	10	47.5	5%	100	C1/C2
44	6	51	5%	100	C1/C2
46	5	49	5%	100	C1/C2
46.5	11.5	42	5%	100	C2
47	0	53	5%	100	C1/C2
53	8	42	5%	100	C2/C3

Example 6 – EPAX5000TG / Cremophor RH40 / Labrasol

Samples were prepared according to Example 2 for the omega-3 fatty acid oil EPAX5000TG and a surfactant system comprising Labrasol and Cremophor RH40 with varying percentages for all three of these components. Table 8 charts the clarity values for this system (placebo) upon 1 to 20 dilution with water as well as 1 to 20 dilution clarity values for the corresponding systems in which 25, 50, 100 and 150 mg of CyA per ml of solution were added.

TABLE 8				
EPAX5000TG %	Labrasol %	Cremophor RH40%	CyA mg/ml	Clarity
5	62	33	n/a	C1
10	15	75	n/a	C1
12	45	43	n/a	C1
15	79	6	n/a	C4
20	38	42	n/a	C1/C2
22	65	13	n/a	C4
27	20	53	n/a	C1/C2
30	56	14	n/a	C4
5	62	33	25	C1
10	15	75	25	C1
12	45	43	25	C1
20	36	42	25	C1
20	27	53	25	C1
5	62	33	50	C1
10	15	75	50	C1
12	45	43	50	C1
20	36	42	50	C1
20	27	53	50	C1
5	62	33	100	C1
10	15	75	100	C1
12	45	43	100	C1
20	36	42	100	C1
20	27	53	100	C1
5	62	33	150	C3
10	15	75	150	C1
12	45	43	150	C2
20	36	42	150	C1
20	27	53	150	C1

Example 7 – EPAX6000FA / Cremophor RH40 / Labrasol

Samples were prepared according to Example 2 for the omega-3 fatty acid oil EPAX6000FA and a surfactant system comprising Labrasol and Cremophor RH40 with varying percentages for all three of these components. Table 9 charts the clarity values for this system (placebo) upon 1 to 20 dilution with water as well as 1 to 20 dilution clarity values for the corresponding systems in which 25, 50, 100 and 150 mg of CyA per ml of solution were added. From analysis of the placebo system, it appears that the greatest amount of oil possible in a microemulsion preconcentrate formulation formulated according to this system is around 27% EPAX6000FA.

TABLE 9

EPAX6000FA %	Labrasol %	Cr m phor RH40%	CyA mg/ml	Clarity
5	62	33	n/a	C1
10	15	75	n/a	C1/C2
12	45	43	n/a	C1/C2
15	79	6	n/a	C2
20	38	42	n/a	C2
22	65	13	n/a	C4
27	20	53	n/a	C2
30	56	14	n/a	C4
40	5	55	n/a	C2/C3
50	5	45	n/a	C4
55	10	35	n/a	C4
50	20	30	n/a	C4
40	32	28	n/a	C4
5	62	33	25	C1
10	15	75	25	C1
12	45	43	25	C1
15	79	6	25	C4
20	38	42	25	C2
22	65	13	25	C4
27	20	53	25	C2
5	62	33	50	C1
10	15	75	50	C1
12	45	43	50	C1
15	79	6	50	C4
20	38	42	50	C1
22	65	13	50	C4
27	20	53	50	C2
5	62	33	100	C4
10	15	75	100	C1
12	45	43	100	C1
15	79	6	100	C4
20	38	42	100	C2
22	65	13	100	C4
27	20	53	100	C3
5	62	33	150	C4
10	15	75	150	C2
12	45	43	150	C3
15	79	6	150	C4
20	38	42	150	C3
22	65	13	150	C4
27	20	53	150	C3

Example 8 –K85TG / Cremophor RH40 / Tween 80 / Labrasol

Samples were prepared according to Example 2 for the omega-3 fatty acid oil K85TG and a surfactant system comprising Labrasol, Cremophor RH40 and Tween 80 (with Cremophor RH40 and Tween 80 held at a 2:1 ratio) with varying percentages for the oil, Labrasol and the Cremophor RH40 and Tween 80 mixture. Table 10 charts the clarity values for this system (placebo) upon 1 to 20 dilution with water. A pseudo-ternary phase diagram showing the microemulsion region (C1, C1/C2, and C2 clarity values) for this placebo system upon 1 to 20 dilution is shown in Figure 1.

TABLE 10				
K85TG %	Labrasol %	Cremophor RH40: Tween 80 (2:1) %	CyA mg/ml	Clarity
48.5	0	51.5	n/a	C4
48.5	8.2	43.3	n/a	C4
48.5	13.7	37.8	n/a	C4
38.8	0	61.2	n/a	C1/C2
38.8	9.9	51.4	n/a	C3
38.8	16.2	45	n/a	C4
31	0	69	n/a	C2
31	11	58	n/a	C2
31	16.4	50.6	n/a	C4
21.7	0	78.3	n/a	C1/C2
21.7	12.6	65.7	n/a	C1/C2
21.7	20.8	57.5	n/a	C1/C2
40	30	30	n/a	C4
35	20	45	n/a	C2
5	10	85	n/a	C1
5	25	70	n/a	C1
5	50	45	n/a	C1
10	30	60	n/a	C1
10	40	50	n/a	C1/C2
15	10	75	n/a	C1
15	15	70	n/a	C2
15	60	25	n/a	C1/C2
20	25	55	n/a	C1/C2
25	35	40	n/a	C4
25	45	30	n/a	C2
35	20	45	n/a	C2
40	30	30	n/a	C4

10

Table 11 charts the 1 to 20 dilution clarity values for the corresponding systems in which 25, 50, 100 and 150 mg of CyA per ml of solution were

added. The pseudo-ternary phase diagram given in Figure 2 shows the microemulsion region for the system upon 1 to 20 dilution having 100 mg/ml CyA per ml of solution.

TABLE 11				
K85TG %	Labrasol %	Cremophor RH40: Tween 80 (2:1) %	CyA mg/ml	Clarity
21.7	0	78.3	100	C1
21.7	12.6	65.7	100	C1
21.7	20.8	57.5	100	C1/C2
31	0	69	100	C1/C2
31	11	58	100	C2
31	16.4	50.6	100	C2/C3
38.8	0	61.2	100	C1/C2
38.8	9.9	51.4	100	C2/C3
38.8	16.2	45	100	C3
48.5	0	51.5	100	C3
48.5	8.2	43.3	100	C3
48.5	13.7	37.8	100	C4

5 *Example 9 –K85TG / Cremophor RH40 / Labrasol*

Samples were prepared according to Example 2 for the omega-3 fatty acid oil K85TG and a surfactant system comprising Labrasol and Cremophor RH40 with varying percentages for all three of these components. Table 12 charts the clarity values for this system (placebo) upon 1 to 20 dilution with water as well as 1 to 20 dilution clarity values for the corresponding systems in which 25, 50, 100 and 150 mg of CyA per ml of solution were added. From an analysis of the placebo system, it appears that the greatest amount of oil possible in a microemulsion preconcentrate formulation formulated according to this system is around 27% K85TG.

15 The microemulsion region on a pseudo-ternary phase diagram obtained by plotting the data for the K85EE/Cremophor/Labrasol system provided in this example is similar to that for the corresponding EPAX5000TG system (Example 6) and the EPAX6000FA system (Example 7) over a range of 0 to 150 mg/ml CyA. The corresponding K85EE system (Example 3)
20 appears to form a larger microemulsion region than the K85TG system.

TABLE12				
K85TG %	Labrasol %	Cremophor RH40%	CyA mg/ml	Clarity
5	62	33	n/a	C1/C2
10	15	75	n/a	C1
12	45	43	n/a	C1
15	79	6	n/a	C4
20	38	42	n/a	C2/C3
22	65	13	n/a	C4
27	20	53	n/a	C2
30	56	14	n/a	C4
5	62	33	25	C1
10	15	75	25	C1
12	45	43	25	C1
20	38	42	25	C2
20	27	53	25	C1
5	62	33	50	C1
10	15	75	50	C1
12	45	43	50	C1
20	38	42	50	C2
20	27	53	50	C1
5	62	33	100	C1
10	15	75	100	C1
12	45	43	100	C1
20	38	42	100	C2
20	27	53	100	C1
5	62	33	150	C2
12	45	43	150	C3
20	38	42	150	C3
27	20	53	150	C1

Example 10 – Mixed Fish Oils / Cremophor RH40 / Tween 80 / Labrasol

- Samples were prepared according to Example 2 for the systems containing a mixture of K85EE and EPAX6000FA and a surfactant system comprising Labrasol, Tween 80 and Cremophor RH40 with varying percentages as described in Table 13. Table 13 charts the clarity values for these systems (placebo) upon 1 to 20 dilution with water as well as 1 to 20 dilution clarity values for the corresponding systems in which 50 or 100 mg of CyA per ml of solution were added.

TABLE 13					
K85EE / EPAX6000F A (2.5:1) %	Cremophor RH40 / Tween 80 (2:1) %	Labrasol %	Clarity (without CyA)	Clarity (with 100 mg CyA)	Clarity (with 50 mg CyA)
21.7	65.7	12.6	C1	C1	C1
31	58	11	C1	C1	C1
38.8	61.2	0	C1/C2	C1/C2	C2
38.8	51.4	9.9	C1/C2	C1/C2	C1/C2
38.8	45	16.2	C1/C2	C1/C2	C1/C2
48.5	51.5	0	C2	C2	C3
48.5	43.3	8.2	C2	C2	C2/C3
48.5	37.8	13.7	C2	C2	C2/C3
50.9	49.1	0	C3	C3	C3
K85EE / EPAX6000F A (5:1) %	Cremophor RH40 / Tween 80 (4:1) %	Labrasol %	Clarity (without CyA)	Clarity (with 100 mg CyA)	Clarity (with 50 mg CyA)
40	55	5	C2	C1/C2	C1
42.5	52.5	5	C1/C2	C1/C2	C1
45	50	5	C1/C2	C1/C2	C1
47	48	5	C2	C2	C1/C2
K85EE / EPAX6000F A (5:1) %	Cremophor RH40 / Tween 80 (2:1) %	Labrasol %	Clarity (without CyA)	Clarity (with 100 mg CyA)	Clarity (with 50 mg CyA)
40	55	5	C1/C2	C1/C2	C1/C2
42.5	52.5	5	C2	C1/C2	C1/C2
45	50	5	C2	C1/C2	C2
47	48	5	C2	C2	C2

Example 11 – Formulations

The following microemulsion preconcentrate formulations according to the instant invention were prepared as follows. The given amounts of cyclosporin, the given amounts of the oil containing omega-3 fatty acid oil, and the given amounts of the surfactant system were stirred until a homogeneous solution was formed. The resulting cyclosporin-containing composition was transferred to a machine for preparing soft capsules and then encapsulated according to conventional methods for producing soft capsules. These products were designed for daily administration, for example administration of 3-8 capsules daily, thus providing both a

therapeutically effective amount of the therapeutic agent cyclosporin A (300 - 800 mg for Formulations 1 and 2 or 75 - 200 mg cyclosporin A for Formulation 3) and a pharmaceutically effective amount of an omega-3 fatty acid oil (1.03 - 2.74 g EPA + DHA for Formulations 1 and 3 or 1.39 - 3.70 g EPA + DHA for Formulation 2) per day. Formulation 4 contains a mixture of omega-3 fatty acid oils as well as minor amounts of a hydrophilic solvent system. Of course, a daily dose may contain combinations of capsules having differing therapeutic agent and/or omega-3 fatty acid oil amounts such as the capsules of Formulations 1, 2, 3 and 4.

Formulation 1

Component	% (wt) of placebo system	wt/capsule
Oil Component:		407 mg
K85EE	37%	(343 mg EPA + DHA)
Surfactant system:		
Cremophor RH40 and Tween 80 (2:1)	53%	583 mg
Labrasol	10%	110 mg
Cyclosporin A		100 mg
		1200 mg total

10

Formulation 2

Component	% (wt) of placebo system	wt/capsule
Oil Component:	50%	550 mg
K85EE		(462 mg EPA + DHA)
Surfactant system:		
Cremophor RH40 and Tween 80 (2:1)	40%	440 mg
Labrasol	10%	110 mg
Cyclosporin A		100 mg
		1200 mg total

Formulation 3

Component	% (wt) of placebo system	wt/capsule
Oil Component:	37%	407 mg
K85EE		(343 mg EPA + DHA)
Surfactant system:		
Cremophor RH40 and Tween 80 (2:1)	53%	583 mg
Labrasol	10%	110 mg
Cyclosporin A		25 mg
		1125 mg total

Formulation 4

Component	% (wt) of system	wt/capsule
Oil component:		
K85EE and EPAX6000FA (2:1)	37.05%	407.55 mg
Surfactant system:		
Cremophor RH40 and Tween 80 (2:1)	49.05%	539.55 mg
Labrasol	9.35%	102.85 mg
Hydrophilic Solvent System		
Ethanol	4.55%	50.05 mg
Cyclosporin A		100.00 mg
		1200 mg total

Additional microemulsion preconcentrate formulations according to the instant invention were also prepared as given below in Table 14. The amount of Cyclosporin A present is given as mg per 1.1 of the preconcentrate (placebo) and the amount of the other components are given as a weight percentage of the preconcentrate (placebo).

TABLE 14								
Formulation No.	5	6	7	8	9	10	11	12
Cyclosporin A	25	25	25	100	25	100	25	100
K85EE	37							
K80EE		37	37	37	37	37	37	37
Cremophor RH40	35.33	35.33	38.67	35.33	38.7	38.7	35.3	35.3
Tween 80	17.67	17.67	19.33	17.67	19.3	19.3	17.7	17.7
Labrasol	10	5		5				
Imwitor 375					5	5	5	5
Ethanol		5	5	5			5	5

Example 12 – Formulations Containing Hydrophilic Solvent Systems

Preconcentrate formulations containing omega-3 fatty acid oil, a surfactant system and more than minor amounts of a hydrophilic solvent system are specified in Table 15. Clarity values for 1 to 50 dilutions of these formulations in a mixture of water and simulated gastric fluid (1:1) are given in Table 15.

TABLE 15								
	Formulation 13		Formulation 14		Formulation 15		Formulation 16	
	mg/cap	%	mg/cap	%	mg/cap	%	mg/cap	%
Therapeutic Agent Cyclosporin A	50	7.0%	50	7.8%	50	7.6%	50	7.4%
Oil Component EPAX6000FA	50	21.1%	50	23.3%	50	22.9%	50	22.1%
K85EE	100		100				100	
K85TG					100		100	
Surfactant System Labrasol	90	51.5%	75	51.1%	75	50.4%	100	48.5%
Myrj-52	130		100		100		75	
Tween 80	75		80		80		80	
Vitamin E-TPGS	70		75		75		75	
Hydrophilic Solvent System Ethanol	50	20.4%	40	17.8%	50	19.1%	50	22.1%
1,2 Propylene Glycol	95		75		75		100	
Clarity	C1		C1		C2		C2	

Additional preconcentrate formulations containing omega-3 fatty acid oil, a surfactant system and more than minor amounts of a hydrophilic solvent system are given below as Formulations 17 and 18.

Formulation 17

Component	% (wt) of system	wt/capsule
Oil component:		
K85EE	5.9%	50mg
EPAX6000FA	11.8%	100 mg
Surfactant system:		
Tween 20	27.9%	237.5 mg
Tween 80	27.9%	237.5 mg
Hydrophilic Solvent System	20.6%*	175 mg
Ethanol		
mg NaOH in 12 ml EtOH)		
Cyclosporin A	5.9%	50 mg
		850 mg total

5 * 0.3% EtOH

Formulation 18

Component	% (wt) of system	wt/capsul
Oil component:		
EPAX5000TG	8.3%	100 mg
EPAX6000FA	16.5%	50mg
Surfactant system:		
Tween 80	12.0%	72.7 mg
Glycerox 767	19.2%	116.4 mg
Vitamin E-TPGS	12.8%	77.3 mg
Hydrophilic Solvent System		
Ethanol	11.7%	70.9 mg
Ethanollic NaOH (66.7 mg NaOH in 1 ml EtOH)	11.3%	68.2mg
Cyclosporin A	8.3%	50 mg
		<hr/> 605.5 mg

Formulations containing fenofibrate, a potent lipid modulator agent, were prepared by mixing the omega-3 fatty acid oil component with the drug powder followed by the addition of the surfactant system and hydrophilic solvent system. The compositions may be prepared at room temperature or heated to 40-50°C to accelerate the solubilization process. Several mixing techniques can be used ranging from mechanical stirring and agitation to sonication. The fenofibrate composition shown below provides a liquid or semi-solid preconcentrate at room temperature.

In vitro testing of the preconcentrates was carried out by diluting the preconcentrate in 50-100 fold water or simulated gastric fluid with gentle mixing or shaking. The aqueous medium temperature varied between 20 and 37°C. Particle size analysis was then carried out using a Nicomp 370. Data reported for Formulation 19 below corresponds to volume weighted distributions.

Formulation 19

Component	Quantity (mg)
Oil component:	
EPAX4510 TG	189
EPAX 6000 FA	95
Surfactant system:	
Tween 80	136
Myrj 52	236
Vitamin E-TPGS	164
Labrasol	127
Hydrophilic Solvent System	
Ethanol	91
1,2-propylene glycol	182
Fenofibrate	100
(mean particle size: 20nm)	

Example 13 – Evaluation of Oral Bioavailability

A two period, two treatment randomised crossover study was designed. Ten (10) healthy male volunteers were recruited into the study and the following treatments were administered during the study: Formulation 5 (25 mg Cyclosporine) and Neoral® (Novartis) (25 mg Cyclosporine). Both treatments were dosed as four 25 mg capsules giving a total dose of 100 mg cyclosporine. Nine (9) subjects successfully completed both treatment periods of this study. Table I6 summarises the mean primary pharmacokinetic parameters for the two treatments.

The results of this study showed that the microemulsion Formulation 5 had a relative bioavailability of 0.81 compared to Neoral® with significantly lower peak cyclosporine blood concentrations. Visual inspection of the individual plots suggested that the initial rate of cyclosporine absorption was slower following administration of the omega-3 oil product.

TABLE 16		
Parameter	Formulations 5	Neoral capsules
Cmax (ng/ml)	392.76 ± 95.93	489.21 ± 98.08
90% CI vs Neoral	66 - 91	
AUC _(0-t) (ng/ml · hr)	1083.44 ± 300.95	1346.92 ± 256.53
90% CI vs Neoral	72 - 86	
AUC _(0-infinity) (ng/ml · hr)	1115.54 ± 302.74	1385.91 ± 244.50
90% CI vs Neoral	72 - 86	
F ratio	0.81 ± 0.16	

The combination of reduced peak blood concentrations along with the inclusion of the omega-3 oil in the microemulsion formulation may result in a reduction of the nephrotoxic side effects of cyclosporine. The relative bioavailability of approximately 80% of Neoral® for this formulation is considerably higher than that reported for the Sandimmun® cyclosporine formulation.

Stability evaluations were undertaken for Formulation 5 at 25°C and 60% relative humidity as well as 40°C and 75% relative humidity. No crystallization occurred under either of these conditions for Formulation 5 through 14 weeks. Upon dilution of the these pre-concentrates, the clarity of the resulting microemulsions remained C1/C2.

A second biostudy was undertaken to evaluate the oral bioavailability of Formulations 6, 7 and 8 compared to Neoral Oral Solution (100 mg). The formulations were packaged in vials and diluted with orange juice prior administration. Ten human subjects completed the study which consisted of four treatment periods.

Table 17 summarises the primary PK parameters for each of the four products administered during the study.

TABLE 17				
Parameter	Formulation 6	Formulation 7	Formulation 8	Neoral Solution
C _{max} (ng/ml)	313.86 ± 68.96	312.86 ± 73.25	335.97 ± 47.38	472.31 ± 89.00
AUC _(0-24h) (ng/ml · hr)	1063.30 ± 301.27	1042.96 ± 306.84	1068.85 ± 258.50	1523.20 ± 313.73
AUC _(0-infinity) (ng/ml · hr)	1123.61 ± 323.66	1111.52 ± 333.47	1121.44 ± 276.67	1595.80 ± 335.58
F ratio*	71.3 ± 19.1	70.2 ± 17.9	72.1 ± 21.5	

* based on AUC_(0-infinity) data

All three products showed very similar bioavailabilities relative to Neoral Solution, approximately 71%. These three products produced good microemulsions of C1/C2 clarity on dilution 1 in 20 with deionized water. The mean particle size of these microemulsions was determined to be 38.7±0.3 nm, 39.1 ±0.1 nm and 39.1 ±0.4 nm (intensity weighted) for Formulation 6, 7 and 8, respectively.

CLAIMS

What is claimed is:

1. A self-emulsifying preconcentrate pharmaceutical composition
5 capable of forming an oil-in-water microemulsion or emulsion upon dilution
with an aqueous solution, comprising:
 - a) a pharmaceutically effective amount of an omega-3 fatty acid
oil;
 - b) a therapeutically effective amount of a poorly water soluble
10 therapeutic agent, wherein the poorly water soluble therapeutic
agent is substantially soluble in the omega-3 fatty acid oil; and
 - c) a surfactant system comprising at least one surfactant;wherein the composition contains minor amounts or is substantially free of a
hydrophilic solvent system.
15
2. The composition of Claim 1, wherein the composition is a
microemulsion preconcentrate.
3. The composition of Claim 1, wherein the composition is an
emulsion preconcentrate.
- 20 4. The composition of Claim 1, wherein the composition is adapted
for oral administration.
5. The composition of Claim 1, wherein the omega-3 fatty acid oil
is present in an amount ranging from 5 to 70% by weight.
- 25 6. The composition of Claim 1, wherein the therapeutic agent is a
cyclosporin.
7. The composition of Claim 1, wherein the omega-3 fatty acid oil
comprises an omega-3 fatty acid oil selected from the group consisting of
EPA, salts of EPA, DHA, salts of DHA, triglycerides of EPA, triglycerides of
30 DHA, ethyl esters of EPA, ethyl esters of DHA and mixtures thereof.

8. The composition of Claim 1, wherein the omega-3 fatty acid oil comprises a component of a fish oil or a mixture of fish oils.

9. The composition of Claim 8, wherein the omega-3 fatty acid component of the fish oil or the mixture of fish oils is at least 50% by weight.

5 10. The composition of Claim 8, wherein the omega-3 fatty acid component of the fish oil or the mixture of fish oils is at least 70% by weight.

11. The composition of Claim 8, wherein the omega-3 fatty acid component of the fish oil or the mixture of fish oils is at least 80% by weight.

12. The composition of Claim 1, wherein the omega-3 fatty acid oil
10 comprises omega-3 fatty acid triglycerides.

13. The composition of Claim 1, wherein the omega-3 fatty acid oil comprises omega-3 fatty acid ethyl esters.

14. The composition of Claim 1, wherein the therapeutic agent is selected from the group consisting of an analgesic, anti-allergic agent, anti-fungal, anti-inflammatory agent, anti-arrhythmic agent, antibiotic, anticoagulant, antidepressant, antidiabetic agent, anti-epilepsy agent, antihypertensive agent, anti-gout agent, anti-malarial, anti-migraine agent, antimuscarinic agent, antineoplastic agent, anti-protozoal agent, anxiolytic, thyroid, anti-thyroid, antiviral, anorectic, bisphosphonate, cardiac inotropic agent, cardiovascular agent, corticosteroid, diuretic, dopaminergic agent, gastrointestinal agent, hemostatic, histamin receptor antagonist, hypnotic, immunosuppressant, kidney protective agent, lipid regulating agent, muscle relaxant, neuroleptic, neurotropic agent, opioid agonist and antagonist, parasympathomimetic, protease inhibitor, prostglandin, sedative, sex
20 hormone, stimulant, sympathomimetic, vasodilator and xanthin or mixtures thereof.

15. The composition of Claim 1, wherein the composition is adapted for topical administration.

16. The composition of Claim 1, wherein the composition is adapted
30 for parenteral administration.

17. A microemulsion or emulsion pharmaceutical composition comprising the self-emulsifying preconcentrate of Claim 1 diluted with an aqueous solution.
18. The composition of Claim 17, wherein the composition is a
5 microemulsion.
19. The composition of Claim 17, wherein the composition is an emulsion.
20. The composition of Claim 17, wherein the composition is adapted for oral administration.
- 10 21. The composition of Claim 17, wherein the therapeutic agent is a cyclosporin.
22. The composition of Claim 17, wherein the omega-3 fatty acid oil comprises an omega-3 fatty acid oil selected from the group consisting of
15 EPA, salts of EPA, DHA, salts of DHA, triglycerides of EPA, triglycerides of DHA, ethyl esters of EPA, ethyl esters of DHA and mixtures thereof.
23. The composition of Claim 17, wherein the omega-3 fatty acid oil comprises a component of a fish oil or a mixture of fish oils.
24. The composition of Claim 23, wherein the omega-3 fatty acid
20 component of the fish oil or the mixture of fish oils is at least 50% by weight.
25. The composition of Claim 23, wherein the omega-3 fatty acid component of the fish oil or the mixture of fish oils is at least 70% by weight.
26. The composition of Claim 23, wherein the omega-3 fatty acid component of the fish oil or the mixture of fish oils is at least 80% by weight.
- 25 27. The composition of Claim 17, wherein the therapeutic agent is selected from the group consisting of an analgesic, anti-allergic agent, anti-fungal, anti-inflammatory agent, anti-arrhythmic agent, antibiotic, anticoagulant, antidepressant, antidiabetic agent, anti-epilepsy agent, antihypertensive agent, anti-gout agent, anti-malarial, anti-migraine agent, antimuscarinic
30 agent, antineoplastic agent, anti-protozoal agent, anxiolytic, thyroid, anti-

thyroid, antiviral, anorectic, bisphosphonate, cardiac inotropic agent, cardiovascular agent, corticosteroid, diuretic, dopaminergic agent, gastrointestinal agent, hemostatic, histamine receptor antagonist, hypnotic, immunosuppressant, kidney protective agent, lipid regulating agent, muscle
5 relaxant, neuroleptic, neurotropic agent, opioid agonist and antagonist, parasympathomimetic, protease inhibitor, prostglandin, sedative, sex hormone, stimulant, sympathomimetic, vasodilator and xanthin or mixtures thereof.

28. The composition of Claim 17, wherein the omega-3 fatty acid oil
10 comprises omega-3 fatty acid triglycerides.

29. The composition of Claim 17, wherein the omega-3 fatty acid oil comprises omega-3 fatty acid ethyl esters.

30. The composition of Claim 17, wherein the composition is adapted for topical administration.

15 31. The composition of Claim 17, wherein the composition is adapted for parenteral administration.

32. The composition of Claim 17, wherein the amount of aqueous solution to preconcentrate is 1:1 or greater.

20 33. A method of lowering the therapeutically effective amount of a poorly water soluble therapeutic agent comprising administering to a human in need of a therapeutically effective amount of the therapeutic agent the self-emulsifying preconcentrate of Claim 1, wherein the omega-3 fatty acid oil exerts an additive effect or synergistic effect to the therapeutic effect of the
25 therapeutic agent.

34. A method of reducing the side effects of a poorly water soluble therapeutic agent comprising administering to a human in need of a therapeutically effective amount of the therapeutic agent the self-emulsifying preconcentrate of Claim 1, wherein the omega-3 fatty acid oil mediates at
30 least one negative side effect of the therapeutic agent.

35. A method of lowering the therapeutically effective amount of a poorly water soluble therapeutic agent comprising administering to a human

in need of a therapeutically effective amount of the therapeutic agent the microemulsion or emulsion of Claim 17, wherein the omega-3 fatty acid oil exerts an additive effect or synergistic effect to the therapeutic effect of the therapeutic agent.

5 36. A method of reducing the side effects of a poorly water soluble therapeutic agent comprising administering to a human in need of a therapeutically effective amount of the therapeutic agent the microemulsion or emulsion of Claim 17, wherein the omega-3 fatty acid oil mediates at least one negative side effect of the therapeutic agent.

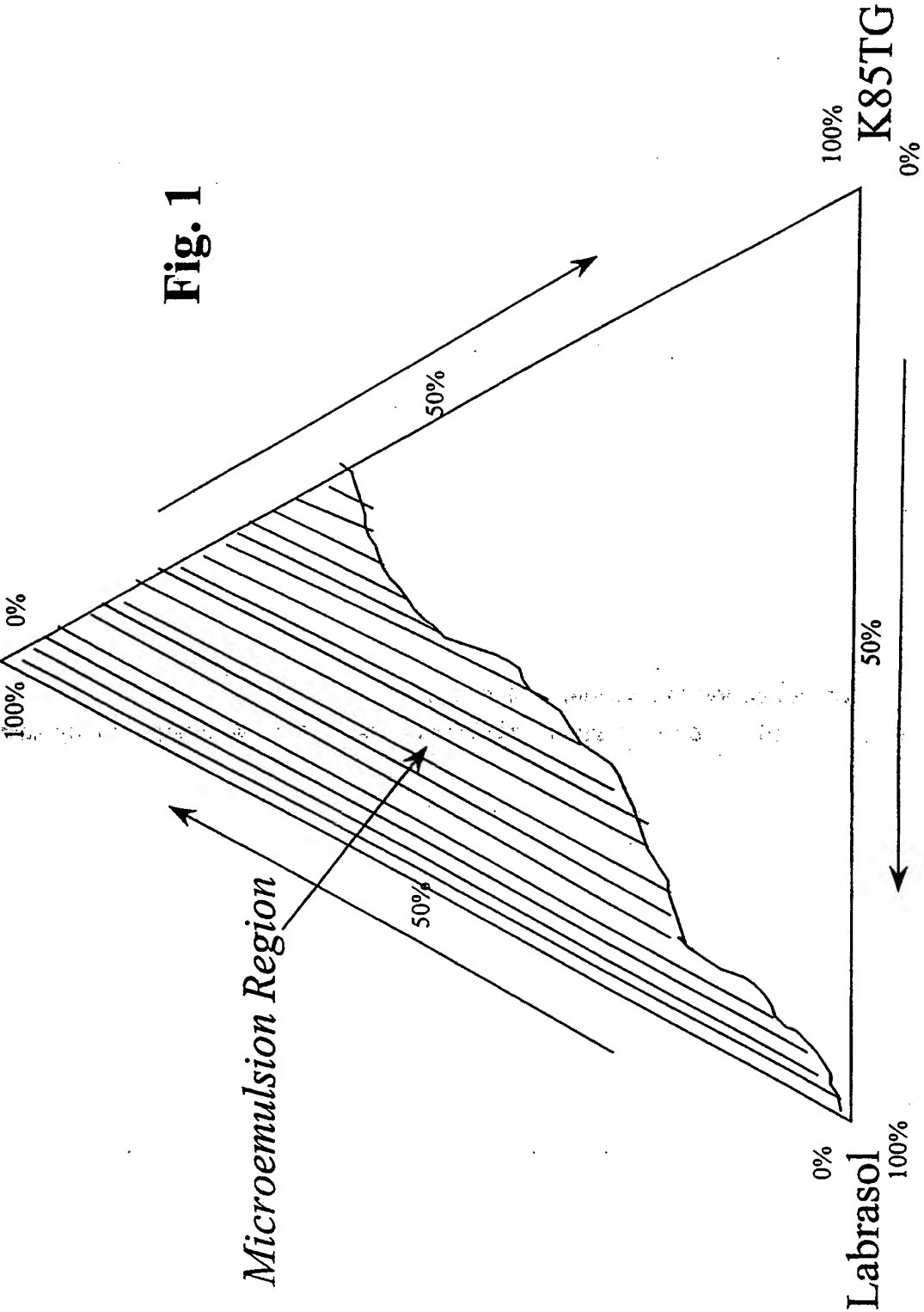
10 37. The method according to any of Claims 33, 34, 35 or 36, wherein the poorly water soluble therapeutic agent is a cyclosporin.

 38. A hard or softgel capsule formulation comprising the composition of Claim 1.

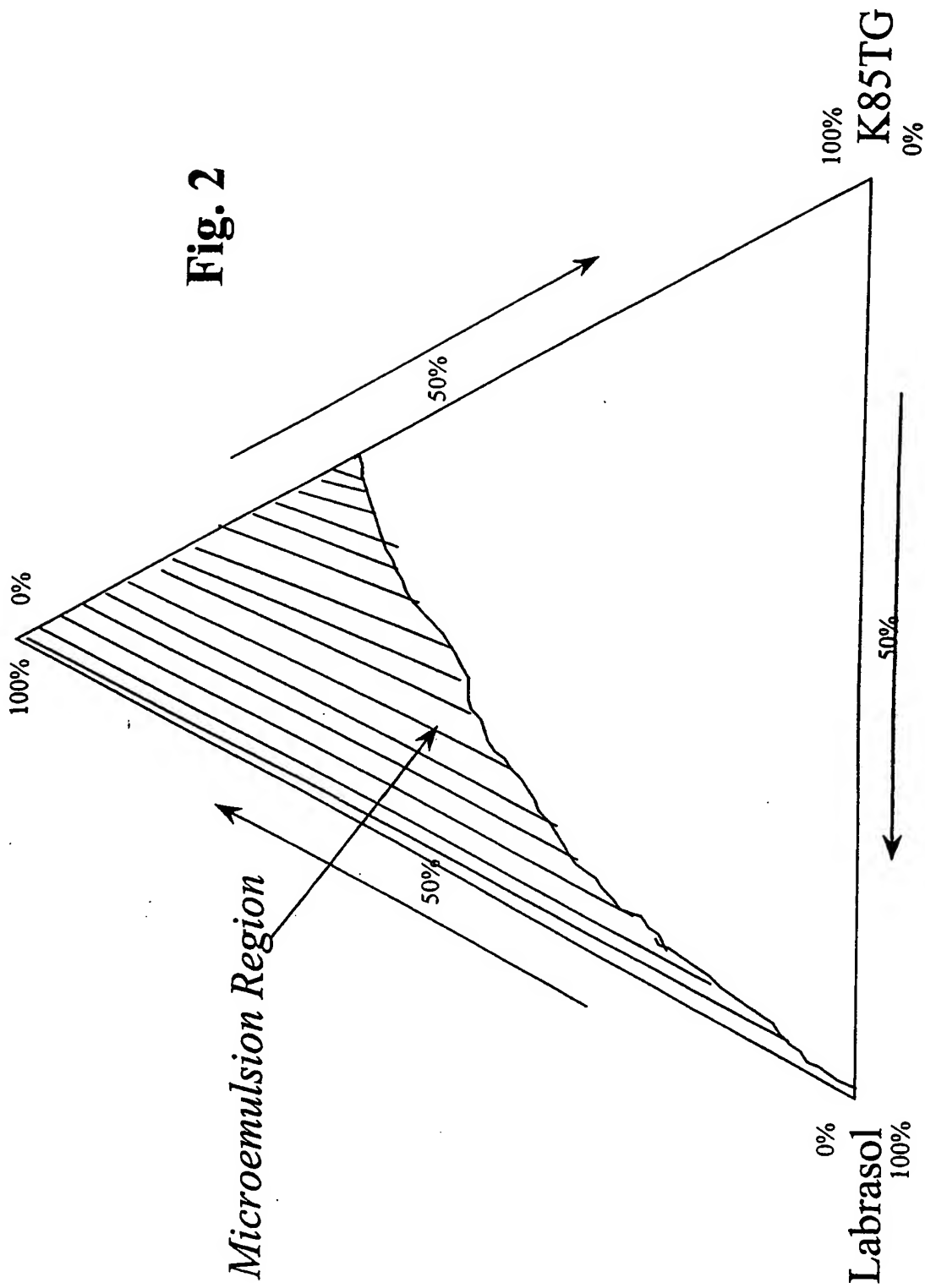
15 39. A self-emulsifying preconcentrate pharmaceutical composition capable of forming an oil-in-water microemulsion or emulsion upon dilution with an aqueous solution, comprising:

- a) a pharmaceutically effective amount of an omega-3 fatty acid oil;
 - b) a therapeutically effective amount of a poorly water soluble therapeutic agent, wherein the poorly water soluble therapeutic agent is substantially soluble in the omega-3 fatty acid oil; and
 - c) a surfactant system comprising at least one surfactant.
- 20

Cremophor : Tween 80 [2:1]



Cremophor : Tween 80 [2:1]



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/26329

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61K 31/20

US CL : 514/560

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/560

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS on-line

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	GB 2 217 173 A (B A WHITTLE) 25 October 1989 (25-10-89), see entire document.	1-5, 7-20, 22-32, 38, 39

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*A document defining the general state of the art which is not considered to be of particular relevance	*X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
*B earlier document published on or after the international filing date	*Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
*L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A document member of the same patent family
*O document referring to an oral disclosure, use, exhibition or other means	
*P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

17 MARCH 1999

Date of mailing of the international search report

02 APR 1999

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

PHYLLIS SPIVACE

Telephone No. (703) 308-1235